McNeil
Consumer & Specialty Pharmaceuticals

JAN 3 1 2005

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

McNeil Consumer & Specialty Pharmaceuticals, a Division of McNeil-PPC, Inc. (McNeil), Fort Washington, PA, submits this Citizen Petition (Petition) under section 505 of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 343.80. McNeil requests that the Commissioner of Food and Drugs approve a change in the professional labeling for aspirin dosing in order to specify the more favorable benefit/risk profile of aspirin doses of 75–150 mg/day for secondary cardiovascular prevention, and 50–150 mg/day for secondary cerebrovascular prevention.

A. ACTION REQUESTED

This Petition requests FDA approval for a change in the professional labeling for aspirin dosing under 21 C.F.R. § 343.80 Labeling Sections, as fully detailed in Appendix 1, in order to specify the more favorable benefit/risk profile of aspirin doses of 75–150 mg/day for secondary cardiovascular prevention, and 50–150 mg/day for secondary cerebrovascular prevention.

Recent studies have clearly demonstrated that the current recommended daily dose in the upper range of 151–325 mg of aspirin for prevention of serious vascular events, has increased risk for gastrointestinal (GI) bleeding, without providing superior benefit as compared to doses of 50–150 mg. The risk of GI bleeding increases monotonically with increasing aspirin doses and, cardiovascular and cerebrovascular disease benefit is no greater at aspirin doses above 150 mg than below 150 mg/day. Lowering the recommended daily dose of aspirin from 75–325 mg to 75–150 mg for secondary cardiovascular prevention and from 50–325 mg to 50–150 mg for secondary cerebrovascular prevention, is in keeping with FDA's Risk Minimization Action Plan[1] and McNeil's long-term goal, to minimize the risk to patients while ensuring beneficial effects.

[1] Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry. Development and use of risk minimization action plans. DRAFT Guidance. May 2004. http://www.fda.gov/cder/guidance/htm. Accessed December 9, 2004.

2005P-0048

CP1

Based on products currently on the market, 81 mg daily dose is the most common dose in the United States (St. Joseph's Aspirin and Low-Dose Bayer) for secondary vascular prophylaxis to provide effective treatment.[2]

Highlights of the requested aspirin dosing changes to the professional labeling are as follows:

- Clinical Studies: Doses of aspirin in the range of 50–150 mg daily have been demonstrated to be as effective as higher doses for the prevention of serious vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death).
- Warnings: GI Side Effects: Aspirin doses of 75–150 mg daily have been shown to have a lower risk of major bleeding events, particularly GI bleeding, when compared with aspirin doses of greater than 150 mg.
- Adverse Reactions: Controlled Trials–Major Bleeding Events: Prospective observations in the context of two clinical trials and two meta-analyses, consistently showed aspirin doses of 75–150 mg daily to have a lower risk of major bleeding events, particularly GI bleeding, when compared with aspirin doses of 151–325 mg.
- Dosage and Administration: The recommended aspirin dose for chronic administration is 75–150 mg daily, which is safe and effective for Prevention of Recurrent Myocardial Infarction (MI), and for Treatment of Unstable Angina Pectoris or Chronic Stable Angina Pectoris; and 50–150 mg daily for Prevention of Ischemic Stroke and Transient Ischemic Attacks (TIA).

McNeil considers that all the material and methods used by the FDA to reach the scientific and regulatory conclusions enunciated in the Federal Register notices of 1988, 1996, and 1998 (Section 2.1.1), as well as the NDA 21-387 approval of new labeling for buffered aspirin (Section 2.1.1), provide the critical background information for consideration of new post-1998 aspirin data, particularly safety data. Using the FDA process to establish the safe and effective dose of aspirin for secondary vascular prevention under 21 C.F.R. § 343.80 Professional Labeling, and the new post-1998 aspirin data, McNeil requests that the professional labeling for aspirin specify the more favorable safety profile of aspirin doses of 75–150 mg daily for secondary cardiovascular prevention, and 50–150 mg daily for secondary cerebrovascular prevention to provide effective treatment and minimize major bleeding events, particularly GI bleeding.

[2] National Drug and Therapeutic Index reports as of October 2004, the 81 mg daily dose is the most recommended aspirin dose for cardiovascular indications representing 57.4% of all primary care physicians.

These conclusions are reflected in the **Clinical Studies**, **Warnings**, **Adverse Reactions-Controlled Trials**, and **Dosage and Administration** sections of the new proposed labeling submitted in the subject Citizen's Petition for FDA's review (Attachment 1). In this petition, McNeil presents scientific evidence that is consistent with the FDA's 1998 established safety and efficacy of aspirin doses of 75–150 mg daily for the cardiovascular prevention effects of aspirin and 50–150 mg daily for the cerebrovascular prevention effects. Further, since doses greater than 150 mg do not provide superior efficacy when compared with doses of 50–150 mg, McNeil asserts that recommending such high doses merely exposes patients to higher incidence of serious GI bleeding events when such safety risks are not warranted.

B. STATEMENT OF GROUNDS

I. EXECUTIVE SUMMARY

The proposed labeling changes in the recommended aspirin dose from 75–325 mg/day to 75–150 mg/day for secondary cardiovascular prevention, and from 50–325 mg/day to 50–150 mg/day for secondary cerebrovascular prevention is supported by published safety data (particularly bleeding data). These data demonstrate that low-dose aspirin results in fewer bleeding complications than higher aspirin doses (>150 mg/day) and published efficacy data demonstrate that doses of aspirin within the range of 50–150 mg/day are equally effective for the prevention of serious vascular events. Clinical studies as well as meta-analyses, substantiate the modifications to the professional labeling for aspirin. These benefit/risk data were identified following an extensive search and review of the literature published between 1996–2004.

- Aspirin Risk: Large clinical trials and meta-analyses have consistently shown that the risk and/or incidence of bleeding complications increase with increasing aspirin dose within the dose range of 50–325 mg/day. While lower doses of aspirin are associated with a lower risk of all bleeding complications, it is the opportunity to reduce the number of severe hemorrhages that provides the most forceful argument for limiting aspirin exposure. Rare but potentially devastating bleeding events, such as severe GI bleeding requiring transfusion or surgery, have profound implications for the affected patient and his or her community. Evidence reviewed in this Citizen's Petition shows that the risk of GI bleeding increases monotonically with increasing aspirin dose. By restricting the daily dose of aspirin to 75–150 mg/day for cardiovascular prevention and 50–150 mg/day for cerebrovascular prevention, patients can minimize their risk for severe bleeding, particularly GI bleeding. Four publications in particular (Peters et al., 2003; Topol et al., 2003; Serebruany et al., 2004; Serebruany et al., 2005 [in press])

collectively show that aspirin doses less than or equal to 150 mg/day result in fewer bleeding complications or lower the risk of bleeding complications compared to aspirin doses greater than 150 mg/day.

- Aspirin Benefit: The proposed labeling change in the recommended aspirin dose, from 50–325 mg/day to 50–150 mg daily, is also supported by published efficacy data demonstrating that doses of aspirin in the range of 50–150 mg/day are equally effective for the prevention of serious cerebrovascular events (non-fatal stroke) and doses of aspirin in the range of 75–150 mg/day are equally effective for the prevention of serious cardiovascular events (non-fatal MI and vascular death). In particular, the Antithrombotic Trialists' Collaboration (ATC) meta-analysis demonstrates that the reduction in the occurrence of serious vascular events across a range of aspirin doses from less than 75 mg/day, 75–150 mg/day, and 500–1500 mg/day in patients at risk of occlusive vascular disease, is similar. Cardiovascular and cerebrovascular disease benefit is no greater at aspirin doses above 150 mg or below 150 mg/day. In addition, the small proportional reduction in events observed in direct comparisons of doses less than 75 mg/day versus greater than or equal to 75 mg/day demonstrates that lower doses of aspirin used in these comparisons are as efficacious as higher doses in this patient population.

In conclusion:

- Labeling changes in the recommended aspirin dose, from 75–325 mg/day to 75–150 mg/day for secondary cardiovascular prevention and from 50–325 mg/day to 50–150 mg/day for secondary cerebrovascular prevention, are supported by safety and efficacy data.
- Low-dose aspirin (50–150 mg/day) demonstrates the most favorable benefit/risk profile when compared to higher doses of aspirin (>150 mg/day), as evidenced by the significantly lower incidence of bleeding complications observed with lower doses, without a corresponding reduction in efficacy.
- Lowering the recommended daily dose of aspirin to 75–150 mg/day for cardiovascular prevention and 50–150 mg/day for cerebrovascular prevention is in keeping with FDA's Risk Minimization Action Plan and with McNeil's long-term goal, to minimize the risk to patients while preserving the benefits.

II. HISTORY OF CARDIOVASCULAR LABELING FOR ASPIRIN

Aspirin for the treatment of acute myocardial infarction (MI) and for the secondary prevention of MI, chronic stable and unstable angina, transient ischemic attacks (TIA), and ischemic stroke, is one of the most important therapies available to reduce cardiovascular

morbidity and mortality. Aspirin has been used extensively worldwide as an analgesic for more than 100 years. The usage has resulted in the accumulation of a significant body of scientific evidence.

The major benefits of aspirin therapy relate to the prevention of certain cardiovascular and cerebrovascular clinical outcomes and the risks relate to the potential adverse events associated with aspirin therapy, such as serious bleeding events, particularly GI bleeding. However, the benefit of low- vs. high-dose aspirin is considered to be a reduction in bleeding outcomes, and the risk of low- vs. high-dose aspirin is considered to be a reduction in the prevention of adverse cardiovascular and cerebrovascular outcomes. Therefore, the benefit/risk ratio is considered favorable if low-dose aspirin (50–150 mg/day) is associated with a lower incidence of bleeding complications, and is found to provide comparable efficacy to high-dose aspirin (>150 mg/day).

A. Rationale for Request for a Change in Aspirin Dosing to the Professional Labeling

Based upon new scientific and clinical data, McNeil requests changes to the professional labeling for aspirin dosing, lowering the aspirin dose upper limit of 325 mg/day to 150 mg/day, in order to specify the more favorable benefit/risk profile of aspirin doses of 75–150 mg/day for cardiovascular prevention and 50–150 mg/day for cerebrovascular prevention. Pursuant to the 1998 Final Rule [63 FR § 56802], the FDA lowered the upper limit of aspirin dosing from 1300 mg/day to 325 mg/day based upon positive findings at lower dosages (e.g. 50, 75, 300 mg daily) along with the higher incidence of side effects expected at the higher dosage (e.g. 1300 mg daily). Clinical studies and meta-analyses subsequent to this ruling, demonstrate that aspirin doses less than or equal to 150 mg/day lower the risk of bleeding, particularly GI bleeds (Table 1). Daily aspirin doses less than or equal to 150 mg continue to provide the cardiovascular and cerebrovascular benefits of higher doses.

Table 1. Published Literature Post-1998 Final Rule Supporting Lower Risk of GI Bleeding

Reference	Aspirin Dose Proving Best Benefit/Risk Profile
Peters et al. (CURE) study. Circulation. 2003;108 (14):1682-1687.	75-100 mg/day
Topol et al. (BRAVO) study. Circulation. 2003;108 (4): 399-406.	75-162 mg/day
Serebruany et al. Am J Hematol. 2004;75:40-7.	<100 mg/day
Serebruany et al. Am J Card. 2005 (in press).[3]	<100 mg/day

B. A Cardiovascular Aspirin Monograph Process

On November 16, 1988, FDA published a notice [53 FR § 46204] of proposed rulemaking in the form of a tentative final monograph (TFM). FDA issued this notice of proposed rulemaking after considering the reports and recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products and the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. Public comments from a variety of sources (e.g., trade associations, drug manufacturers, healthcare professionals, etc.) regarding the advance notices of proposed rulemaking for OTC internal analgesic, antipyretic and antirheumatic drug products were also considered. The tentative final monograph established conditions under which OTC internal analgesic, antipyretic, and antirheumatic drug products are generally recognized as safe and effective and are therefore, not misbranded. In addition to issues affecting OTC labeling of aspirin, the tentative final monograph proposed to expand the professional labeling to include preliminary cardiovascular and cerebrovascular indications for aspirin, and specifically recommended the following two indication statements:

"For reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. There is inadequate evidence that aspirin or buffered aspirin is effective in reducing TIA's in women at the recommended dosage. There is no evidence that aspirin or buffered aspirin is of benefit in the treatment of completed strokes in men or women"; and

"To reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous myocardial infarction or unstable angina pectoris."

[3] Publication date May, 2005.

With regard to dosing, in the 1988 Federal Register notice, FDA concluded that aspirin at a dose of 1300 mg/day was safe and effective for reducing the risk of recurrent transient ischemic attacks or stroke in men. For secondary MI prevention, the notice [53 FR § 46232] stated in part:

"Dosage and Administration: Although most of the studies used dosages exceeding 300 milligrams, 2 trials used only 300 milligrams, and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 milligrams, or a conventional 325 milligram aspirin dose is a reasonable, routine dose . that would minimize gastrointestinal adverse reactions."

Based on findings from the Aspirin Myocardial Infarction Study (AMIS Research Group, 1980)[4] regarding adverse reactions, in the 1988 Federal Register Notice, the FDA also stated [53 FR § 46231] in part:

"Gastrointestinal Reactions: Doses of 1,000 milligrams per day of aspirin caused gastrointestinal symptoms and bleeding that in some cases were clinically significant."

Since the initial proposed rule of November 16, 1988 [53 FR § 46204] for aspirin professional labeling, the FDA has reviewed the safety experience associated with the use of aspirin over a broad range of effective doses (i.e., 50–1500 mg/day) and has expanded the vascular indications and refined aspirin dosage instructions both in 1996 and 1998.

On June 13, 1996, FDA published a proposed amendment to the tentative final monograph of 1988 [61 FR § 30002]. In this proposal, FDA recognized the dose-relationship between aspirin dose and major bleeding events. Regarding bleeding events in the AMIS trial (1980)[4], in which subjects received aspirin at a dose of 1000 mg/day, and the Second International Study of Infarct Survival (ISIS-2) (1988)[5], in which subjects received aspirin at a dose of 162.5 mg/day, the Agency stated [61 FR § 30008] in part:

"Bleeding: In the AMIS and other trials, aspirin-treated subjects had increased rates of gross gastrointestinal bleeding. In the ISIS-2 study, there was no significant difference in the incidence of major bleeding (bleeds requiring transfusion) between 8,587 subjects taking 162.5 milligrams aspirin daily and 8,600 subjects taking placebo."

In the October 23, 1998 Final Rule [63 FR § 56802], the last professional labeling change for aspirin was made in which FDA codified the acute MI indication and refined its

[4] AMIS Research Group (Aspirin Myocardial Infarction Study). A randomized controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA.* 1980;243:661-669.
[5] ISIS-2 Collaborative Group (Second International Study of Infarct Survival). Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute Myocardial Infarction: ISIS-2. *Lancet.* 1988;2:349-360.

evaluation of the dose needed for secondary prevention following the availability of new data and analyses. FDA considered data from the Antiplatelet Trialists' Collaboration (1994)[6], the United Kingdom-TIA study (1988)[7], the Danish Very Low Dose study (1988)[8], the Swedish Aspirin Low-dose Trial (1991)[9], European Stroke Prevention Study-2 (ESPS-2) for TIA or stroke prevention (1996)[10], and the Swedish Angina Pectoris Aspirin Trial (SAPAT) in chronic stable angina (1992).[11] The Agency provided the following summary [63 FR § 56806] regarding support for a lower dose of aspirin:

"*In summary, there is clinical trial support for a lower dose of aspirin for subjects with a history of TIA or cerebral ischemia and considerable evidence in patients with MI. It is also clear that the effect of aspirin on platelet functions is complete at lower doses. The positive findings at lower dosages (e.g., 50, 75 and 300 mg daily) along with the higher incidence of side effects expected at the higher dosage (e.g., 1300 mg daily) are sufficient reasons to lower the dosage of aspirin for subjects with TIA and stroke.*"

Furthermore, in the 1998 Final Rule, FDA also stated [63 FR § 56805] in part:

"...specific doses for specific uses of aspirin, supported by appropriate data, are necessary for an optimal benefit to the user and, in general, that a minimum effective dose established for a given indication should be used to minimize dose related adverse effects."

C. Aspirin Labeling – New Drug Application (NDA) Process

Since the 1998 Final Rule notice, the approved monograph for professional labeling of aspirin was used as part of the basis for the New Drug prescription labeling of buffered aspirin approved as an independent drug product co-packaged with PRAVACHOL® (pravastatin sodium). This product, PRAVIGARD™ PAC (NDA 21-387), was approved by FDA on June 24, 2003. The aspirin component of that labeling was consistent with the 1998 Final Rule and provides physicians with information appropriate to the use of buffered aspirin when used in conjunction with PRAVACHOL®. FDA's approval of PRAVIGARD™

---

[6] Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ.* 1994;308:81–106.

[7] UK-TIA Study Group. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. *BMJ.* 1988;296:316–320.

[8] Boysen G, Sorensen PS, Juhler M, et al. Danish very-low-dose aspirin after carotid endarterectomy trial. *Stroke.* 1988;19:1211–1215.

[9] SALT collaborative group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet.* 1991;338:1345–1349.

[10] Diener C, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurological Sciences.* 1996;143(1-2):1-13.

[11] Juul-Möller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina 10/7/2004 12:32 PMPectoris Aspirin Trial (SAPAT) Group. *Lancet.* 1992;340:1421–1425.

PAC was consistent with the monograph professional labeling of aspirin. However, the FDA review resulted in modification of the aspirin component of that labeling. McNeil's proposal includes a request to modify the current professional labeling to be consistent with FDA's aspirin evaluation during the PRAVIGARD™ PAC review.

III. SCIENTIFIC EVIDENCE SUPPORTS LOWER BLEEDING RISK OF 75–150 MG ASPIRIN

A. Published Literature Search Methodology – Safety Data

Three literature searches were conducted for aspirin-related publications for the time period 1996–2004. The search strategies and methodologies are detailed in Attachment 2. Figure 1 presents the flow chart of the search methodology. A total of 850 articles were reviewed in detail for relevant content. Of the 850 publications, 72 articles included an aspirin-alone treatment group and presented clinically relevant bleeding event information.

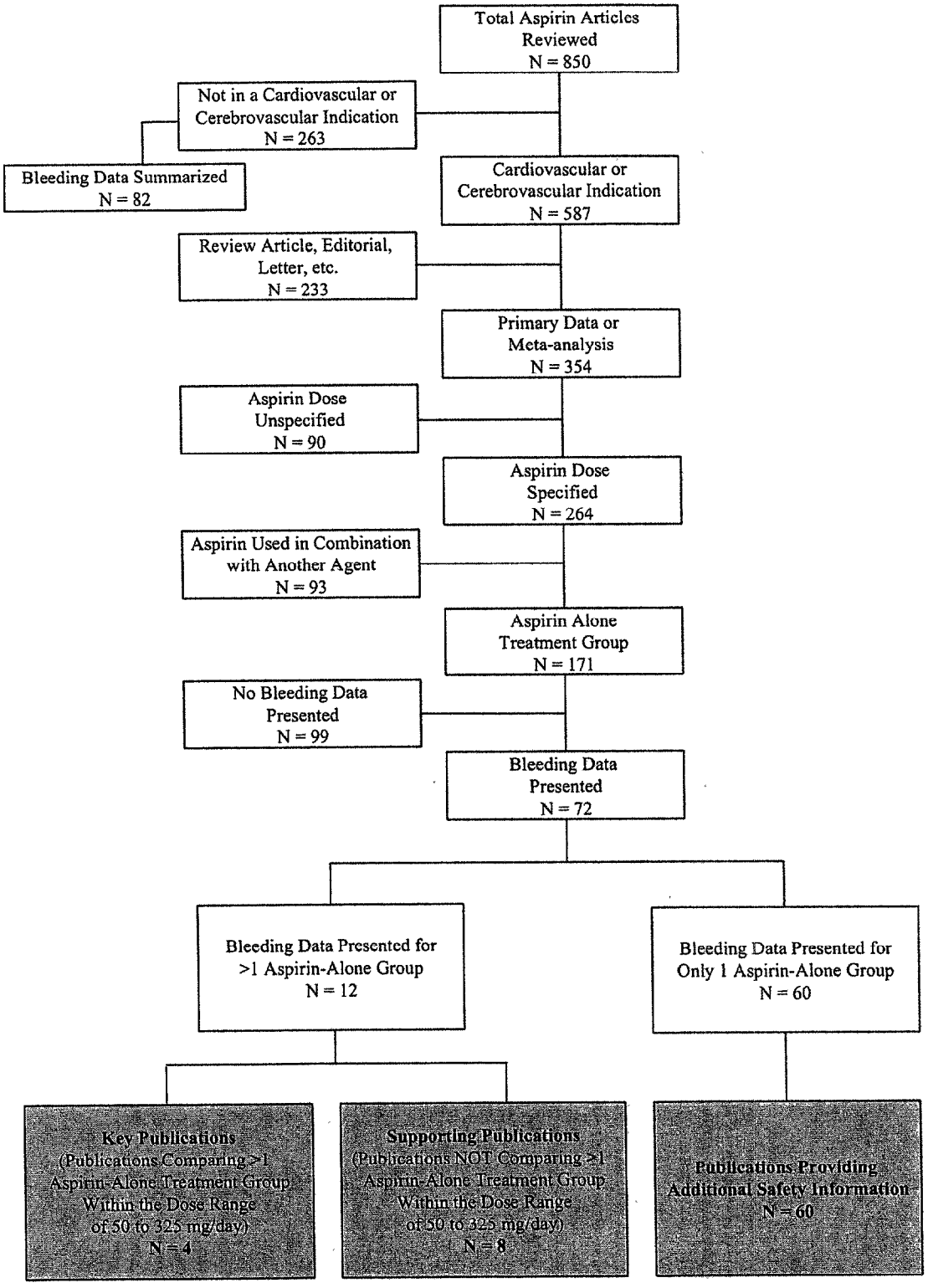
Per the FDA's 1998 Final Rule for the Professional Labeling of Aspirin under 21 C.F.R. § 343.80, the current Dosage and Administration recommendations identify aspirin doses within the range of 50–325 mg/day for the following cardiovascular and cerebrovascular indications: ischemic stroke and TIA, suspected acute MI, prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris, CABG, and percutaneous transluminal coronary angioplasty (PTCA). For the purpose of this Petition, McNeil further identifies the aspirin dose(s) within the range of 50–325 mg/day that confers the most favorable benefit/risk profile for aspirin in terms of bleeding complications, particularly gastrointestinal bleeding.

The 72 articles included in the aspirin safety summary (Attachment 2) are classified into three major groupings. The first two groupings include articles that reported bleeding outcome information for more than one aspirin-alone treatment group, allowing for a dose-by-dose comparison of safety. The first of these groupings comprises four articles summarizing the results of clinical trials or meta-analysis in which direct comparisons of bleeding outcome data were made between at least two aspirin-alone treatment groups that feel within the dose range of 50–325 mg/day. This grouping forms the basis of this Petition and the proposed labeling change in the recommended aspirin dose from 75–325 mg/day to 75–150 mg/day for cardiovascular prevention and from 50–325 mg/day to 50–150 mg/day for cerebrovascular prevention.

The second grouping comprises eight articles summarizing the results of clinical trials, meta-analyses, or other studies that either compared bleeding outcome data for one-aspirin alone treatment group outside the dose-range of interest, or compared bleeding outcome

data for aspirin-alone treatment groups that all fell outside the dose range of interest. The third grouping comprises 60 articles summarizing the results of clinical trials, meta analyses, or other studies in which bleeding outcome data were presented for a single aspirin-alone treatment group, thereby not allowing for direct comparisons between aspirin doses. The inclusion of this third publication grouping in this Petition serves to ensure that all aspirin-related safety data in cardiovascular and/or cerebrovascular indications published since 1996 are presented. However, these studies were conducted in a wide variety of indications, many of which are not directly relevant to this Petition.

Figure 1. Flowchart of Literature Search Methodology – Safety Data



B. Detailed Analysis of the Scientific Publications in Support of Less GI Bleeding With Daily Use of 75–150 mg Aspirin

The key safety publications include clinical trials or meta-analyses in which direct comparisons of bleeding outcome data were made between at least two aspirin-alone treatment groups that fell within the dose range of 50–325 mg/day. The grouping comprises two large clinical trials (a post-hoc analysis of the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) trial [Peters et al. 2003][12] and the Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion Trial (BRAVO) trial [Topol et al., 2003])[13] and two large-scale meta-analyses (Serebruany et al., 2004; Serebrauny et al., 2005 [in press]).[14,15] The general characteristics of these four publications are presented in Table 2. Detailed safety analysis of these studies and other supporting studies are discussed in Attachment 2.

[12] Peters RJD, Mehta SR, Fox KAA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. *Circulation.* 2003:108(14):1682-1687.

[13] Topol EJ, Easton D, Harrington RA et al. Randomized, double-blind, placebo-controlled, international trial or the oral Iib/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. *Circulation.* 2003:108(4)399-406.

[14] Serebruany VL, Malinin AI, Eisert RM et al. Risk of bleeding complications with antiplatelet agents; Meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. *Amer J Hematol.* 2004:75(1):40-47.

[15] Serebruany VL, Steinhubl SR, Berger PB, et al. The risk of bleeding after different doses of aspirin: A post-hoc analysis of 192,036 patients enrolled in 31 randomized controlled trials. *Am J Card.* 2005 (in press).

Table 2. Key Safety Publications

Reference	Total Subjects (N)	Patient Population	Treatment Groups (N)	Aspirin Treatment Duration	Mean Age (years)	Type of Evidence
Peters RJG, Mehta SR, Fox KAA, Zao F, Lewis BS, Kopecky L, Diaz R, Commerford PJ,Valentin V, Yusuf. (CURE) study. Circulation. 2003;108 (14):1682-1687.	12,562	Patients with symptoms of ACS without ST-segment elevation >1 mm on the ECG	Aspirin 75–100 mg/day[15] alone or with 75 mg/day clopidogrel (5320)[17] (Male: 58.8%; Female: 41,2%) Aspirin 101–199 mg/day[16] alone or with 75 mg/day clopidogrel (3109)[17] (Male: 61.1%; Female: 38.9%) Aspirin 200–325 mg/day[16] alone or with 75 mg/day clopidogrel (4110)[17] (Male: 65.4%; Female: 34.6%)	Mean: 9 months	64.2	Clinical Trial
Topol EJ, Easton D, Harrington RA, Amarenco P, Califf RM, Graffagnino C, Davis S, Diener H, Ferguson J, Fitzgerald D, Granett J, Shuaib A, Koudstaal PJ, Theroux P, Van der Wolf F, Sigmon K, et al., (BRAVO) study. Circulation. 2003;108 (4): 399-406.	9190	Patients with coronary or cerebrovascular disease	Aspirin 75–162 mg/day[16] + placebo (2410) (Male: 65.4; Female: 34.6) Aspirin >162 mg/day[16] + placebo (2179) (Male: 65.4; Female: 34.6) Aspirin 75–325 mg/day[16] + lotrafiban 30 or 50 mg[18] BID (4600) (Male: 65.4; Female: 34.6)	Maximum of 2 years	62.2	Clinical Trial
Serebruany VL, Malinin AI, Eisert RM, Sane DC. American Journal of Hematology. 2004;75:40-7	338,191	Patients with multiple cerebrovascular/ cardiovascular conditions	Aspirin <100 mg/day[19] Aspirin 100–325 mg/day[19] Aspirin >325 mg/day[19] Dipyridamole[19] ADP-receptor blockers[19] Glycoprotein IIb/IIIa inhibitors, i.v.[19] Glycoprotein IIb/IIIa inhibitors, oral[19]	ns[20]	ns	Meta-analysis of clinical trials
Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Oshrine BR, Baggish JS, Bhatt DL, Topol EJ. Am J Card. 2005 (in press).[3]	192,036	Patients with multiple cerebrovascular/ cardiovascular conditions	Aspirin <100 mg/day Aspirin 100-200 mg/day Aspirin >200 mg/day	ns[20]	ns	Meta-analysis of clinical trials

[16] *The choice of aspirin dose was determined by the Investigator.*
[17] Patients in the CURE study were randomized to receive clopidogrel or placebo plus aspirin. In the analysis by Peters et al. included in this table, patients from the CURE study were divided into treatment groups by aspirin dose (≤100, 101–199, and ≥200 mg/day) (total of 6 treatment groups). The number of patients were only given for the combined treatment groups at each aspirin dose (e.g., clopidogrel + aspirin ≤100 mg/day vs. aspirin alone). Number of patients for the aspirin alone treatment groups were not included in the article.
[18] The dose of lotrafiban was dependent on age and creatinine clearance.
[19] The number of patients in each treatment group were not specified.
[20] Only trials in which patients had a clinical follow-up for at least one month were included in the analysis.

1. Peters et al., 2003 (CURE Study)

Peters et al. (2003)[12] conducted a post-hoc observational analysis of the CURE study, a randomized, double-blind, placebo-controlled study that was designed to evaluate the benefits and risks of adding clopidogrel to different doses of aspirin in patients with ACS. The risk of major and minor bleeding at various aspirin doses was assessed.

A total of 12,562 patients from 28 countries were enrolled in the study. To be included in the study, patients had to have symptoms indicative of ACS within 24 hours of study entry without ST-segment elevation greater than 1 mm on the electrocardiogram (ECG). In addition, ECG evidence of new ischemia or concentrations of cardiac enzymes (including troponin) at two times the upper limit of normal (ULN) was required.

Patients were assigned to receive clopidogrel or placebo. A loading dose of 300 mg oral clopidogrel or placebo was given, followed by 75 mg/day clopidogrel or placebo. Aspirin was coadministered with both clopidogrel and placebo. The dose of aspirin was left to the discretion of the investigator, but a 75–325 mg/day dose was recommended per the protocol. Patients were treated for an average of 3–12 months (mean: 9 months). The CURE study recruited patients from 482 centers in 28 countries. An average of 89% of all patients per center used a dose of aspirin within 50 mg of the most frequently used dose.

Bleeding endpoints measured included major bleeding, which was defined as significantly disabling, intraocular bleeding leading to significant loss of vision, or bleeding requiring transfusion of two or three units of red blood cells or equivalent whole blood. Major bleeding was subclassified as life-threatening or other major bleeding. Life-threatening bleeding complications were defined as fatal or leading to a drop in hemoglobin of greater than or equal to 5 g/dL or significant hypotension with the need for inotropes, requiring surgery (other than vascular site repair) or symptomatic intracranial hemorrhage, or requiring transfusion of four or more units of red blood cells or equivalent whole blood. Minor bleeding was defined as any other bleeding requiring modification of the drug regimen.

As shown in Table 3, in the aspirin plus placebo group (i.e., aspirin-alone), the incidence of major bleeding increased significantly with increasing aspirin dose (1.9%, 2.8%, and 3.7% for aspirin doses of 75–100, 101–199, and 200–325 mg/day, respectively; p-value for trend, < 0.0001). When bleeding complications were further classified as life-threatening, a similar trend was observed in bleeding incidence (1.3%, 1.9%, and 2.4%, for aspirin doses

of 75–100, 101–199, and 200–325 mg/day, respectively; p-value for trend, 0.004). The adjusted odds ratios (OR) of developing a major bleeding complication were higher when aspirin-alone doses of 101–199 mg/day (OR: 1.52; 95% CI: 1.00 to 2.31) and 200–325 mg/day (OR: 1.70; 95% CI: 1.22 to 2.59) were compared to doses 75–100 mg/day. A similar pattern was observed for life-threatening bleeding complications.

Table 3. Percent Incidence of Major and Life-Threatening Bleeding by Various Doses of Aspirin[12]

	Aspirin-alone (% incidence)	Aspirin +Clopidogrel (% incidence)
Major Bleeding Complications		
Aspirin 75–100 mg/day	1.86	2.97
Aspirin 101–199 mg/day	2.82	3.41
Aspirin 200–325 mg/day	3.67	4.86
P-value for trend	<0.0001	<0.001
Adjusted[21] OR for 101–199 mg/day vs. 75–100 mg/day	1.52 (1.00 to 2.31)	1.20 (0.84 to1.73)
Adjusted[21] OR for 200–325 mg/day vs. 75–100 mg/day	1.70 (1.22 to 2.59)	1.63 (1.19 to 2.23)
Life-threatening[21] Bleeding Complications		
Aspirin 75–100 mg/day	1.26	1.75
Aspirin 101–199 mg/day	1.90	1.39
Aspirin 325–200 mg/day	2.37	3.29
P-value for trend	0.004	0.0006
Adjusted[22] OR for 101–199 mg/day vs. 75–100 mg/day	1.48 (0.89 to 2.46)	0.79 (0.47 to 1.32)
Adjusted[22] OR for 200–325 mg/day vs. 75–100 mg/day	1.64 (1.04 to 2.59)	1.82 (1.22 to 2.71)

Abbreviations: OR = odds ratio

For the aspirin + clopidogrel group, a similar proportionate increase in major bleeding complications (3.0%, 3.4%, and 4.9%, p-value for trend, <0.001) and life-threatening bleeding complications (1.8%, 1.4%, and 3.3%, p-value for trend, 0.0006) was observed. Across both treatment groups, a trend for a higher risk of major bleeding with increasing aspirin dose was observed in patients undergoing percutaneous coronary intervention, coronary artery bypass grafting, or no revascularization (data not shown).

[21] Defined as fatal bleeding or bleeding leading to a decrease in hemoglobin of ≥ 5g/dL or significant hypotension with the need for inotropes, requiring surgery (other than vascular site repair) or symptomatic intracranial hemorrhage, or requiring transfusion of 4 or more units of red blood cells or equivalent whole blood.
[22] Adjusted for gender, weight, hypertension, components of the TIMI risk score, rates of angiography, PCI and CABG, and the use of NSAIDs, heparin, GP IIb/IIIa inhibitors, oral anticoagulants, open-label ticlopidine, or clopidogrel at any time during the study period.

In sum, the data show that the risk of major bleeding increased with increasing aspirin dose irrespective of whether it was used alone or in combination with clopidogrel. Patients with acute coronary syndromes taking aspirin doses between 75–100 mg/day demonstrated a lower risk associated with bleeding complications than in patients taking aspirin doses of 101–199 mg/day and aspirin doses of 200–325 mg/day, respectively.

2. Topol et al., 2003 (BRAVO Study)

The BRAVO study was a randomized, double-blind, placebo-controlled, study of lotrafiban, an oral GP IIb/IIIa antagonist, in patients with coronary and/or cerebrovascular disease.[13] Safety endpoints included the incidence of serious bleeding, any bleeding, or any transfusion.

A total of 9190 patients from 23 countries were enrolled in the study. Patients were included if they had a prior MI or unstable angina within 14 days of baseline, ischemic stroke 5–30 days after the acute event, a TIA within 30 days, or "double bed" vascular disease defined as documented peripheral vascular disease combined with either coronary or cerebrovascular disease.

A total of 4589 patients in the placebo plus aspirin treatment groups of the BRAVO study were exposed to doses of aspirin that ranged from 75–325 mg/day for up to two years (75–162 mg/day: 2410 patients; >162 mg/day: 2179 patients). A dose reduction was required in 4.6% of patients in this treatment group and 22.9% of patients prematurely discontinued study medication. Reasons for premature discontinuation included major (1.6%) and minor (2.6%) bleeding. The length of follow-up was a median of 366 days (includes patients in both the placebo plus aspirin and lotrafiban plus aspirin treatment groups; 25th and 75th percentiles, respectively, were 279 and 463 days in the placebo plus aspirin treatment groups). Follow-up was for up to two years.

As shown in Table 4, when the safety endpoints were evaluated by aspirin dose (low: 75-162 mg/day vs. high: >162 mg/day), the incidence of serious bleeding (2.4% vs. 3.3%), any bleeding (11.1% vs.15.4%), or any transfusion (1.0% vs. 2.0%) was lower among subjects receiving 75–162 mg/day aspirin compared to greater than 162 mg/day aspirin, respectively. Serious bleeding was also more common among patients exposed to higher aspirin doses (>162 mg/day) than lower doses when given with lotrafiban (data not shown). The authors of this publication suggest that lower aspirin doses (≤162 mg/day) may be the most practical way to lower bleeding risk in patients with cardiovascular or cerebrovascular disease.

Table 4. Bleeding and Other Outcomes by Aspirin Dose in the Placebo (Aspirin-alone) Treatment Group[13]

Event	75–162 mg/day (N = 2410)	>162 mg/day (N = 2179)
Serious Bleeding (% incidence)	2.4	3.3
Any Bleeding (% incidence)	11.1	15.4
Transfusion (% incidence)	1.0	2.0

Although the dose of aspirin was not randomly assigned in the BRAVO study, the finding of increased bleeding with doses greater than 162 mg/day was noteworthy. Based on the BRAVO study, doses of aspirin of less than or equal to 162 mg/day are prudent to avoid bleeding complications.[13]

3. Serebruany et al., 2004

Serebruany et al. (2004)[14] conducted a meta-analysis of 50 randomized clinical trials to assess the risk of hemorrhage associated with various antiplatelet agents: aspirin less than 100 mg/day, aspirin greater than or equal to 100 mg/day, dipyridamole, thienopyridines, and intravenous and oral GP IIb/IIIa inhibitors.[14] Table 5 provides a listing of the aspirin trials. Data from clinical trials published between 1988–2002 retrieved from MEDLINE™, OVID™, and CARDIOSOURCE™ included patients with a follow-up of at least one month, and a full description of hemorrhagic complications were included in the analysis. The 50 clinical trials contributed a total of 338,191 patients, approximately 85% of whom were enrolled in the United States. Most of the patients had acute coronary syndrome, unstable angina or MI. A few trials involved hypertensive patients, and about 40% of trials included patients with percutaneous coronary intervention. Hemorrhagic events were classified by the publication authors.

Table 5. Aspirin Clinical Trials Analyzed in Meta-Analysis[14]

Trial	Number of Patients Enrolled	Number of Patients on Aspirin (Dose)	Aspirin Dose (mg)
DUTCH TIA	3,131	1,576	30
		1,576	286
ACE	2,849	698	81
		697	325
		703	650
		706	1300
SAPAT	2,035	1,009	75
HOT	18,790	9,399	75
ESPS-2	6,602	1,649	50

Table 5. Aspirin Clinical Trials Analyzed in Meta-Analysis[14]

Trial	Number of Patients Enrolled	Number of Patients on Aspirin (Dose)	Aspirin Dose (mg)
SALT	1,360	676	75
SYMPHONY-2	6,671	2,231	160
SYMPHONY	9,172	3,074	160
STAMI	1,470	736	160
SARSI	1,965	557	325
CURE	12,562	6,303	75-325
CAST	21,106	10,554	160
EAFT	1,007	404	300
IST	19,435	9,720	325
PEP	13,359	6,679	160
UK-TIA	2,435	810	300
US NURSE	87,678	87,678	325
PHSRG	22,071	11,037	325
SPAF-II	1,100	545	325
ISIS-2	17,187	8,587	325
CAPRIE	19,185	9,586	325
TASS	3,069	1,540	1200

Patients in this meta-analysis were exposed to aspirin doses less than 100 mg/day (range: 30–81mg/day), 100–325 mg/day, or greater than 325 mg/day (range: 650–1300 mg/day). A total of 14,986 patients were exposed to less than 100 mg/day aspirin. Most of the patients exposed to aspirin were taking between 100–325 mg/day (160,774). A total of 3764 patients were exposed to daily aspirin doses greater than 325 mg. The duration of exposure was not specified, but can be obtained for the 50 individual clinical trials comprising this analysis and referenced in this publication. Only trials in which patients had a clinical follow-up for at least one month were included in the analysis.

The purpose of this meta-analysis was to determine the frequency of bleeding complications dependent on the class and dose of antiplatelet used. A total of 50 randomized controlled trials with a total of 338,191 patients were analyzed. Aspirin doses were divided into three groups: less than 100, 100–325, and greater than 325 mg/day. Bleeding complications analyzed by this meta-analysis included major and minor bleeding events, hemorrhagic stroke, GI bleeding events, and total bleeding events. The weighted average bleeding rates across aspirin dose groups were analyzed as shown in Table 6 below.

Table 6. Weighted Average Bleeding Rates by Aspirin Dose

Aspirin Dose (mg/day)	Number of Trials Reported	Number of Patients	Bleeding Rate (%)	95% CI
Major Bleeding				
<100 mg	5	13,337	1.7	1.4 to 1.9
100-325 mg	11	43,489	1.7	1.5 to 1.8
>325 mg	2	1409	2.5	1.7 to 3.3
Minor Bleeding				
<100 mg	3	11,963	1.8	1.5 to 2.0
100-325 mg	5	13,588	6.5	6.1 to 6.9
>325 mg[23]	0	0	Not applicable	Not applicable
Hemorrhagic Stroke				
<100 mg	4	12,661	0.3	0.2 to 0.4
100-325 mg	15	152,955	0.3	0.2 to 0.3
>325 mg	3	2224	1.1	0.7 to 1.5
GI Bleeding				
<100 mg	5	13,337	1.1	0.9 to 1.3
100-325 mg	7	30,413	2.4	2.2 to 2.6
>325 mg	3	2224	2.5	1.8 to 3.1
Total Bleeding				
<100 mg	4	12,639	3.6	3.3 to 3.9
100-325 mg	6	22,745	9.1	8.7 to 9.4
>325 mg	1	1540	9.9	8.4 to 11.4

With increased aspirin dose, the weighted average rate for major bleeding episodes increased from 1.7% at the less than 100 mg/day and 100–325 mg/day dose groups to 2.5% with aspirin doses greater than 325 mg/day. A similar trend was observed for hemorrhagic stroke (0.3% at the <100 and 100–325 mg/day doses and 1.1% at doses >325 mg/day). A more pronounced dose-related increase was observed regarding the rates of GI and minor bleeding. The GI bleeding rates were 1.1, 2.4, and 2.5%, for aspirin doses less than 100, 100–325, and greater than 325 mg/day, respectively, and the minor bleeding rates were 1.8 and 6.5% at the less than 100 mg and 100–325 mg/day dose groups, respectively. Of note, no trials reported minor bleeding events for the greater than 325 mg/day dose. The rate for all bleeding events was 3.6%, 9.1%, and 9.9% for the low, middle, and high-dose aspirin groups, respectively.

[23] No trials reported minor bleeding events for this dose range.

In this analysis, low-dose aspirin therapy (defined in this meta-analysis as <100 mg/day) was associated with the lowest risk of total bleeding events of any antiplatelet used in the studies comprising this meta-analysis. These data demonstrate that higher doses of aspirin (≥ 100 mg/day) were associated with relatively higher hemorrhagic rates. Thus, based on the results of this meta-analysis, the risk of a patient developing bleeding episodes (e.g., GI and total) increases with increasing aspirin dose. Patients taking doses of less than 100 mg/day of aspirin, had significantly lower rates of bleeding episodes than those patients taking doses of 100–325 mg/day and both groups had lower rates of bleeding episodes than patients taking aspirin doses greater than 325 mg/day.

4. Serebruany et al., 2005 (in press)

The objective of this study was to determine and compare the risk of hemorrhage for the low (<100 mg/day), moderate (100–200 mg/day), and high (>200 mg/day) doses of aspirin. Data from clinical trials published 1988–2003 in English were retrieved from MEDLINE™, OVID™, and CARDIOSOURCE™. Only those studies in which patients had clinical follow-up for at least one month and in which a detailed description of hemorrhagic complications was reported were included. Information on sample size, study design, duration, aspirin dose, patient characteristics and bleeding severity was independently and blindly reviewed. Data from 31 clinical trials with a total of 192,036 patients met the quality criteria, and were analyzed. Patients were divided into three groups dependent on their aspirin daily dose: low (<100 mg), nine trials; moderate (100–200 mg), eight trials; and high (>200 mg/day), 21 trials. The bleeding complications were classified as major (22 trials), minor (12 trials), hemorrhagic stroke (22 trials), GI (12 trials), fatal/life threatening (9 trials), and total (12 trials) (Table 7). About 63% of the patients were enrolled in the United States.

Table 7. Aspirin Clinical Trials Analyzed in Meta-Analysis[14]

Trial	Number of Patients Enrolled	Number of Patients on Aspirin (Dose)	Bleeding Events Total	Bleeding Events GI
Aspirin <100 mg/day				
DUTCH TIA	3131	1555	89	14
ESPS-2	6602	1649	135	--
SAPAT	2035	1009	27	11
HOT	0	9399	292	102
TPT	5499	1268	--	5
SALT	1369	676	49	9
CURE	6303	948	35	6
ACE	2849	698	--	8
PPP			24	17
Aspirin 100-200 mg/day			--	--
2nd SYMPHONY	6671	2231	--	--
SYMPHONY	9172	3074	570	--
STAMI	1470	736	--	--
PEP	13359	6679	--	--
CARS	8803	3281	--	--
CAST	21106	10554	--	--
CHAMP	5059	2357	--	--
CURE	6303	3311	152	13
Aspirin >200 mg/day				
DUTCH TIA	313	1576	137	21
EAFT	1007	404	--	10
AFASAK 2	677	169	31	--
MUST	622	153	--	--
UK-TIA	2435	810	--	25
STARS	1965	557	10	--
ACE	2849	697	--	6
IST	19435	9720	--	--
US NURSE	87678	87678	--	--
PHSRG	22071	11037	--	364
SPAF-II	1100	545	--	--
ISIS-2	17187	8587	--	--
CAPRIE	19185	9586	890	255
CREDO	2116	1063	--	--
WARSS	2206	1103	--	--
SPAF-III	892	892	--	--
CURE	6303	2044	297	28
ACE	2849	703	--	8
TASS	3069	1540	152	--
ACE	2849	706	--	8
UK-TIA	2435	815	--	39

As shown in Table 8, low dose aspirin (<100 mg/day) was associated with the lowest risk of bleeding (major –1.56%, minor – 4.9%, hemorrhagic stroke – 0.24%, GI – 0.97%, fatal/life threatening – 0.27%, total – 3.72%). Moderate daily dose of aspirin (100–200 mg/day) was

associated with the low risk for major (1.54%), GI (0.39%), and fatal/life threatening (0.46%) bleeding complications, while the rate of minor (6.75%) and total (11.31%) hemorrhagic events was relatively high. The greatest rate of bleeding complications was associated with the higher aspirin doses (>200 mg/day), however the hemorrhagic stoke were significantly higher (p=0.007) in the 100–200 mg/day cohort.

Table 8. Weighted Average Bleeding Rates by Aspirin Dose

Aspirin Dose (mg/day)	Number of Trials Reported[24]	Number of Patients	Bleeding Rate (%)	95% CI
Major Bleeding				
<100 mg	8	17,202	1.56	1.2 to 1.8
100–200 mg	8	32,223	1.54	1.4 to 1.8
>200 mg	10	19,758	2.29	1.9 to 7.0
Minor Bleeding				
<100	5	14,179	4.9	1.4 to 2.1
100–200 mg	4	10,973	6.75	6.1 to 7.0
>200 mg	6	6,359	8.86	4.7 to 11.2
Hemorrhagic Stroke				
<100 mg	7	17,103	0.24	0.1 to 0.4
100–200 mg	5	21,527	0.647	0.2 to 0.5
>200 mg	15	136,122	0.21	0.7 to 1.5
GI Bleeding				
<100 mg	8	17,779	0.97	0.7 to 1.3
100–200 mg	1	3,311	0.39	Not applicable
>200 mg	7	28,378	2.69	1.8 to 3.1
Fatal/Life Threatening				
<100 mg	5	13,276	0.27	0.1 to 0.4
100–200 mg	3	16,222	0.46	0.3 to 0.8
>200 mg	5	7,233	1.59	0.7 to 2.2
Total Bleeding				
<100 mg	7	17,462	3.72	3.1 to 3.7
100–200 mg	2	6,385	11.31	8.9 to 13.2
>200 mg	6	15,472	9.8	7.2 to 10.8

[24] Trials Analyzed – 31; Aspirin <100 mg = 9 trials (19,428 patients); Aspirin 100-200 mg = 8 trials (32,223 patients); Aspirin >200 mg = 18 trials (140,385 patients; Total patients analyzed = 192,036.

Despite substantial differences in the reporting patterns of bleeding complications, low dose (<100 mg/day) aspirin was associated with the lowest risk. Aspirin doses of less than or equal to 200 mg/day caused fewer major bleeding events, particularly GI bleeding events, when compared with doses greater than 200 mg (equivalent to 325 mg in the United States). Surprisingly, doses of aspirin between 100–200 mg/day caused a relatively high hemorrhagic event rate, especially with regard to minor, GI, hemorrhagic stroke, and total bleeding. Similar results were reported in previous studies[12,13,26], but Serebruany et al., (2005, in press) extends the bleeding observations to a larger cohort, and refines the optimal dose of aspirin with respect to bleeding.

C. Safety Conclusions

- Although adverse events have been reported at low aspirin doses, within the dose range of 50–325 mg/day, more bleeding events occur at higher doses (i.e., >150 mg daily) than at lower doses (i.e., 75–150 mg daily).
- The recommended aspirin dose for chronic administration is 75–150 mg daily, which is safe and effective for prevention of recurrent MI, and for treatment of unstable angina pectoris or chronic stable angina pectoris, and 50–150 mg daily for treatment of ischemic stroke and TIA. Aspirin is recommended for patients who undergo revascularization procedures, such as coronary artery bypass grafting (CABG), angioplasty, or carotid endarterectomy, if there is a pre-existing condition for which aspirin is already indicated. Therapy should be continued indefinitely.

IV. SCIENTIFIC EVIDENCE DEMONSTRATES COMPARABLE EFFICACY OF 50–150 MG ASPIRIN

Published efficacy data demonstrate that doses of aspirin within the range of 50–150 mg/day are equally effective for the prevention of serious vascular events (non-fatal MI, non-fatal stroke and vascular death). These efficacy data were identified following an extensive search and review of the literature published between 1996–2004. Data from the most relevant study, the Antithrombotic Trialists' Collaboration (ATC) meta-analysis, is presented in this efficacy summary. Also, presented in Attachment 3, are supportive studies[25], each of which provide efficacy outcome information resulting from comparisons of two or more aspirin dosing groups of patients with cardiovascular- and/or cerebrovascular-related illnesses.

[25] Detailed summaries of the six supportive efficacy studies are found in Attachment 3.

The efficacy results from publications presented in this efficacy summary support the proposed labeling change in the recommended aspirin dose from 50–325 mg/day to 50–150 mg/day in that lower doses are as effective as higher doses, with low dose demonstrating a lower incidence of serious bleeding events (in particular, GI bleeding).

A. Literature Search Methodology – Efficacy Data

Three literature searches were conducted for aspirin-related publications for the time period 1996–2004. The search strategies and methodologies are detailed in Attachment 3. A flowchart of the literature search methodologies is found in Figure 2. A total of 850 articles were reviewed in detail for relevant content. Of the 850 publications, 106 articles presented clinically relevant efficacy outcome information.

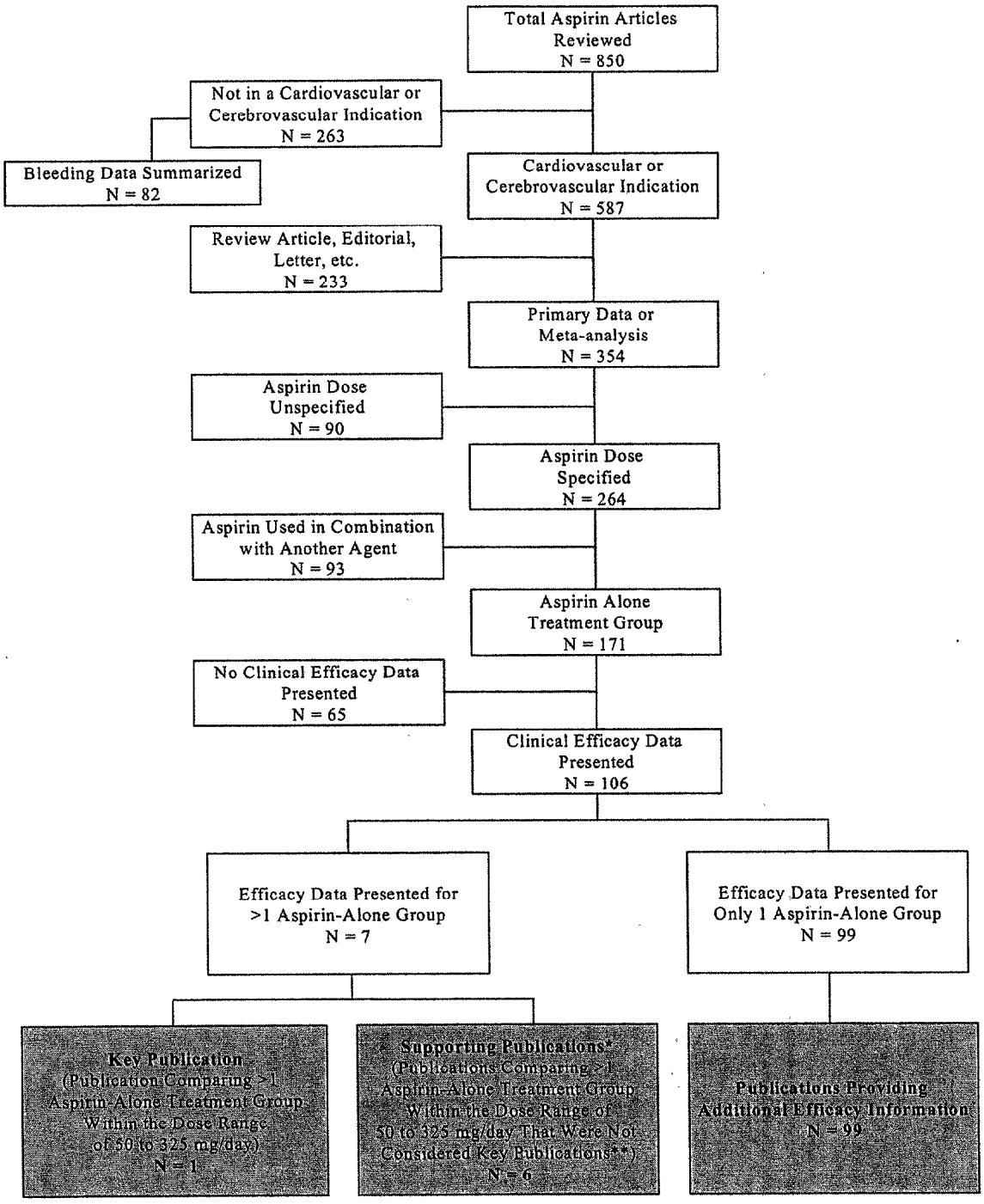
Per the FDA's 1998 Final Rule for the Professional Labeling of Aspirin under 21 C.F.R. § 343.80, the current Dosage and Administration recommendations identify aspirin doses within the range of 50–325 mg/day for the following cardiovascular and cerebrovascular indications: ischemic stroke and TIA, suspected acute MI, prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris, CABG, and percutaneous transluminal coronary angioplasty (PTCA). For the purpose of this Petition, McNeil further identifies the aspirin dose(s) within the range of 50–325 mg/day that confers the most favorable benefit/risk profile for aspirin in terms of bleeding complications, particularly gastrointestinal bleeding.

The 106 articles included in the Integrated Summary of Efficacy (Attachment 3) are classified into three major groupings. The first two groupings include articles that reported efficacy outcome information for more than one aspirin-alone treatment group, allowing for a dose-by-dose comparison of safety. The first of these groupings comprises one article summarizing the results of a meta-analysis in which direct comparisons of efficacy outcome data were made between at least two aspirin-alone treatment groups that fell within the dose range of 50–325 mg/day. This grouping forms the basis of this Petition and the proposed labeling change in the recommended aspirin dose of 50–325 mg/day to 50–150 mg/day.

The second grouping comprises six articles summarizing the results of clinical trials, meta-analyses, or other studies that either (1) compare efficacy outcome data for at least two aspirin-alone treatment group outside the dose-range of interest, or compared bleeding outcome data for aspirin-alone treatment groups that fell within the dose range of 50–325

mg/day but the study design provided indirect support, or (2) did not compare efficacy outcome data between at least two aspirin-alone treatment groups that fell within the dose range of interest. The third grouping comprises 99 articles summarizing the results of clinical trials, meta analyses, or other studies in which efficacy outcome data were presented for a single aspirin-alone treatment group, thereby not allowing for direct comparisons between aspirin doses. The inclusion of this third publication grouping in this Petition serves to ensure that all aspirin-related efficacy data in cardiovascular and/or cerebrovascular indications published since 1996 are presented. However, these studies were conducted in a wide variety of indications, many of which are not directly relevant to this Petition.

Figure 2. Flowchart of Efficacy Literature Search Methodologies



* The Supporting Publications grouping also includes publications that did not compare >1 aspirin-alone treatment group within the dose range of 50 to 325 mg/day.

** These publications were not considered Key Publications primarily due to study design issues.

B. Detailed Analysis of the Scientific Publications in Support of Comparable 50–150 mg Aspirin Efficacy

Per the FDA's 1998 Final Rule for the Professional Labeling of Aspirin, the current Dosage and Administration recommendations identify aspirin doses within the range of 50–325 mg/day for the following cardiovascular and cerebrovascular indications: ischemic stroke and TIA, suspected acute MI, prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty (PTCA). For the purposes of this efficacy summary, McNeil sought to further identify the aspirin dose(s) within the range of 50–325 mg/day that confer the most favorable efficacy profile for aspirin. The efficacy results from publications presented in this efficacy summary support the proposed labeling change in the recommended aspirin dose from 50–325 mg/day to 50–150 mg/day in that lower doses are as effective as higher doses, with low dose demonstrating a lower incidence of serious bleeding events (in particular, GI bleeding).

1. Antithrombotic Trialists' Collaboration, 2002 (ATC)

The key efficacy publication from the review period, is the Antithrombotic Trialists' Collaboration (2002)[26], a large meta-analysis in which direct comparisons of efficacy outcome data were made between at least two aspirin-alone treatment groups that fell within the dose range of 50–325 mg/day. Results from the ATC form the basis of this efficacy summary. This meta-analysis included a total of 212,000 patients from 287 randomized trials who were at increased risk of occlusive vascular events. Comparisons of different aspirin doses comprise some of the most convincing data to date that low daily doses of aspirin (75–150 mg/day) are at least as effective as higher daily doses (≥160 mg/day) in reducing the incidence of non-fatal MI, non-fatal stroke, and vascular death (Table 9). The primary objective of the analysis was to determine the effects of aspirin and other antiplatelet therapies among patients at high annual risk (over 3% a year) of vascular events based on evidence of pre-existing disease (previous occlusive event or predisposing condition).

[26] Antithrombotic Trialist' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002; 324(7329):71-86.

Table 9. Table of Publications – Key Efficacy Publication

Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329) 71-86.	212,000	Patients at high risk of occlusive vascular events	Antiplatelet regimen vs. control (135,000) Different antiplatelet regimens (77,000) Aspirin dose: (<75 mg to 1500 mg/day)[27]	ns[28]	Meta-analysis[29]

Analyses were based on data from 197 studies involving 135,000 patients where antiplatelet therapy was compared to a non-antiplatelet control group, and from 90 studies involving 77,000 patients where comparisons were made between different antiplatelet therapies. Aspirin was the most widely studied antiplatelet drug. The primary measure of outcome was a "serious vascular event" (i.e., non-fatal myocardial infarction, non-fatal stroke, or death from a vascular or unknown cause [most deaths in high risk patients are likely to be due to vascular causes]). Deaths were divided into those with a vascular cause (cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, other vascular, or unknown cause) and those that were considered to be definitely non-vascular in nature. Strokes were subdivided into intracranial hemorrhages (intracerebral, subdural, subarachnoid, and extradural hemorrhages) and strokes of ischemic or unknown etiology.

Table 10 represents exposure data for the comparisons relevant to this efficacy summary. In the meta-analyses using data from clinical trials in which different aspirin doses were compared to controls, a total of 29,652 patients from 65 trials were exposed to doses of aspirin that ranged from less than 75 to 500–1500 mg/day, as shown in Table 10. Meta-analyses using data from clinical trials in which more than one aspirin dose was investigated included a total of 6767 patients from 10 clinical trials. These patients were exposed to aspirin doses greater than or equal to 75 mg/day versus 75–325 mg/day or 500–1500 mg/day versus 75–325 mg/day.

[27] Doses of antiplatelet therapies and controls used in individual studies included were not specified.
[28] Duration of treatment of antiplatelet therapies used in studies included in the ATC meta-analysis was not specified in the article. Of note, trials that included oral antiplatelet regimens were eligible for inclusion in the meta-analysis only if they had assessed >1 day of treatment. Trials of parenteral administration of antiplatelet regimens of any duration were included.
[29] Studies that were believed to have used a randomization method and that contained two randomized groups that differed only with respect to the antiplatelet comparison of interest were included in the ATC meta-analysis.

Table 10. Summary of Subject Accountability and Exposure to Aspirin – ATC, 2002

Reference	N[30]	Aspirin Doses[30]	Number of Patients Exposed[30]		Duration of Exposure
ATC, 2002	29,652	<75 mg/day 75–150 mg/day 160–325 mg/day 500–1500 mg/day	1827[31] 3370[31] 13,240[31] 11,215[31]		ns
	6767	≥75 mg/day vs. 75–325 mg/day[32]	1795[33]	1775[33]	ns
		500–1500 mg/day vs. 75–325 mg/day[34]	1608[33]	1589[33]	

Comparison of the incidence of vascular events across 65 trials (59,395 patients) in which different aspirin doses were compared to controls (no aspirin) revealed that no particular range of aspirin dose greater than or equal to 75 mg/day provided additional benefit for the prevention of serious vascular events (Table 11). The proportional reduction (percent odds reduction) in vascular events was similar for doses of 75–150 mg/day (32%), 160–325 mg/day (26%), and 500–1500 mg/day (19%), demonstrating that there is no difference in the occurrence of vascular events in patients treated with 75–150 mg/day versus higher doses of aspirin. At doses less than 75 mg/day, the odds reduction was comparable (the 95% CIs overlapped), but that one must keep in mind that there were only three studies in this dosage group.

[30] Exposure data presented are from 2 separate comparisons presented in the ATC. The first included meta-analyses using data from clinical trials in which different aspirin doses were compared to controls (N=29,652). The second included meta-analyses using data from clinical trials in which more than one aspirin dose was investigated (N=6767). Data presented represents patients exposed to aspirin only.

[31] The total numbers of patients exposed to aspirin in this meta-analysis were not specified, but were derived from a figure in the publication. This number only includes patients exposed to aspirin in trials in which aspirin was compared to a control group. This number includes patients from trials that may have contributed to more than one aspirin-alone dose comparison group.

[32] Includes 2 trials comparing 75–325 vs. <75 mg/day and 1 trial of 500–1500 vs. <75 mg/day

[33] Represents number of patients in each aspirin treatment regimen (e.g., ≥75 mg/day vs. 75–325 mg/day).

[34] Includes 1 trial comparing 1400 vs. 350 mg/day and another (excluding patients with acute stroke) comparing 1000 vs. 300 mg/day among patients who were also given dipyridamole.

Table 11. Incidence and Proportional Reduction in Vascular Events From Comparisons of Different Aspirin Doses Versus Controls[35]

Trial Category	Number of Trials	Number of Vascular Events/Number Exposed (%)		% Odds Reduction (SE)
		Aspirin	Adjusted Control[36]	
<75 mg/day	3	316/1827 (17.3)	354/1828 (19.4)	13 (8)
75–150 mg/day	12	366/3370 (10.9)	517/3406 (15.2)	32 (6)
160–325 mg/day	19	1526/13240 (11.5)	1963/13273 (14.8)	26 (3)
500–1500 mg/day	34	1621/11215 (14.5)	1930/11236 (17.2)	19 (3)
Any dose[37]	65	3829/29652 (12.9)	4764/29743 (16.0)	23 (2)

In sum, the results of these analyses from the ATC verify that lower doses of aspirin (50–150 mg/day) are as effective as higher doses in preventing serious vascular events among high-risk patients.

C. Efficacy Conclusions

- Doses of aspirin within the range of 50–150 mg daily are equally effective for the prevention of serious vascular events (non-fatal MI, non-fatal stroke, and vascular death).
- The recommended aspirin dose for chronic administration is 75–150 mg daily, which is safe and effective for prevention of recurrent MI, and for treatment of unstable angina pectoris or chronic stable angina pectoris, and 50–150 mg daily for treatment of ischemic stroke and TIA. Aspirin is recommended for patients who undergo revascularization procedures, such as coronary artery bypass grafting (CABG), angioplasty, or carotid endarterectomy, if there is a pre-existing condition for which aspirin is already indicated. Therapy should be continued indefinitely.

[35] Includes data from high-risk patients except those with acute stroke. Only meta-analyses involving 500 patients or more are represented in the table.
[36] Controls include patients who did not receive aspirin.
[37] Some trials contributed to more than 1 comparison.

IV. CONCLUSIONS

Data from publications discussed in the safety summary substantiate the following safety claims for aspirin:

- Although adverse events have been reported at low aspirin doses, within the dose range of 50–325 mg/day, more bleeding events occur at higher doses (i.e., >150 mg daily) than at lower doses (i.e., 75–150 mg daily).
- The recommended aspirin dose for chronic administration is 75–150 mg daily, which is safe and effective for prevention of recurrent MI, and for treatment of unstable angina pectoris or chronic stable angina pectoris, and 50–150 mg daily for treatment of ischemic stroke and TIA. Aspirin is recommended for patients who undergo revascularization procedures, such as coronary artery bypass grafting (CABG), angioplasty, or carotid endarterectomy, if there is a pre-existing condition for which aspirin is already indicated. Therapy should be continued indefinitely.

Data from the meta-analysis discussed in the efficacy summary is consistent with the FDA's previous conclusions [63 FR § 56806]:

- Doses of aspirin within the range of 50–150 mg daily are equally effective for the prevention of serious vascular events (non-fatal MI, non-fatal stroke, and vascular death).

Lowering the recommended daily dose of aspirin to 75–150 mg for secondary cardiovascular prevention and to 50–199 for secondary cerebrovascular prevention is safe and effective and in keeping with FDA's Risk Minimization Action Plan[1] to minimize the risk to patients while preserving the benefits.

C. ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), McNeil will provide data concerning the economic impact of the relief requested should such information be requested by FDA.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petitioner.

Respectfully yours,

MCNEIL CONSUMER & SPECIALTY PHARMACEUTICALS

William L. McComb
President